

# **Traumatic Hemorrhage, Resuscitation, Adjuncts to Hemostasis**

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# Objectives

- **Briefly discuss diagnosis and management of traumatic hemorrhagic shock**
- **Present a current overview of hemostasis**
- **Discuss Recombinant Factor VIIa**

# Massive Hemorrhage

## ● Definition of massive hemorrhage

- Loss of one blood volume over 24 hours
- Loss of 50% blood volume over 3 hours
- Loss of 150 mL per minute

# Massive Hemorrhage

- **Total blood volume for 70 kg adult**  
 $.07 \times 70 \text{ kg} = 4.9 \text{ liters}$
- **50% of total blood volume for 70 kg adult**  
 $.50 \times 4.9 \text{ liters} = 2.45 \text{ liters}$
- **40% of total blood volume for 70 kg adult**  
 $.40 \times 4.9 \text{ liters} = 1.96 \text{ liters}$

**Note: An acute loss of 40% blood volume is immediately life threatening!**

# Estimated Blood Loss (initial presentation)

Blood loss	≤15%	15-30%	30-40%	>40%
HR (bpm)	< 100	> 100	> 120	> 140
BP	Normal	Normal	Decreased	Decreased
PP	Normal	Decreased	Decreased	Decreased
RR	14-20	20-30	30-40	>35
Urine	>30	20-30	5-15	Negligible
CNS	Normal	Anxious	Confused	Lethargic

## Responses to Initial Fluid Resuscitation\*

	Rapid Response	Transient Response	No Response
<b>Vital Signs</b>	Return to normal	Transient improvement; recurrence of ↓BP and ↑HR	Remain abnormal
<b>Estimated Blood Loss</b>	Minimal (10% - 20%)	Moderate and ongoing (20% - 40%)	Severe (> 40%)
<b>Need for More Crystalloid</b>	Low	High	High
<b>Need for Blood</b>	Low	Moderate - high	Immediate
<b>Blood Preparation</b>	Type and crossmatch	Type-specific	Emergency blood release
<b>Need for Operative Intervention</b>	Possibly	Likely	Highly likely
<b>Surgical Consultation</b>	Yes	Yes	Yes

\*2000 mL Ringer's lactate in adults, 20 mL/kg Ringer's lactate in children, over 10 to 15 minutes.

# Traumatic Shock

- **Step One: Identify cause**
- **Step Two: Correct mechanical causes**
- **Step Three: Control hemorrhage**
- **Step Four: Resuscitate**
  - **Give fluid**
  - **Assess results**

# **Diagnosis of Hemorrhage**

- 1. Chest**
- 2. Abdomen**
- 3. Retroperitoneum**
- 4. Long bones**
- 5. The “street”**



# Diagnosis of Hemorrhage

- **Chest:** CXR, chest tube, CT scan
- **Abdomen:** FAST, CT scan, diagnostic lavage, operating room
- **Retroperitoneum:** CT scan
- **Long bone compartments:** physical examination, radiography
- **The street:** patient, paramedic or witness accounts, physical examination

# Massive Hemorrhage

## Mortality versus units of blood transfusion

- Mortality 28% if received 10 to 19 units
- Mortality 65% if received 20 to 39 units
- Mortality 83% if received 40 or more units
- Average mortality 47% if  $> 10u$  PRBC

Wilson WK et al. *Am Surg.* 1987;53:310-317

# Mortality following Blood Transfusion



- # prbc's transfused is *independent predictor* of worse clinical outcome

- Corwin HL, *et al*: the CRIT study: anemia and blood transfusion in the critically ill - current clinical practice in the US. *Crit Care Med* 2004;32:39

- ICU organ dysfunction and mortality higher in pts with more transfusions

- Vincent JL, *et al*: Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288:1499

- Transfusion is associated with nosocomial infections

- Taylor RW, *et al*: Impact of allogenic prbcs on nosocomial infection rates in the critically ill patient. *Crit Care Med* 2002;30:2249.

- # and age of prbcs transfused are independently associated with mortality

- Malone DL, *et al*: Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma*. 2003; 54:898.

# **Early Management: Anesthesia**

- **Supportive fluid resuscitation**
  - **Avoid acute exsanguination**
  - **Minimize risk of organ system failure**
  - **Facilitate hemostasis**
- **Preservation of homeostasis:**
  - **Temperature**
  - **Pulmonary function**

# Goals for resuscitation:

## Early

- Systolic BP 80-100 mmHg
- Heart rate < 120 bpm
- Pulse oximeter working
- Urine output present
- Mentation adequate
- pH > 7.20
- Hematocrit > 25%

McCunn M, Dutton R: Endpoints of Resuscitation. *Curr Opin Anes* 2001

# Goals for resuscitation:

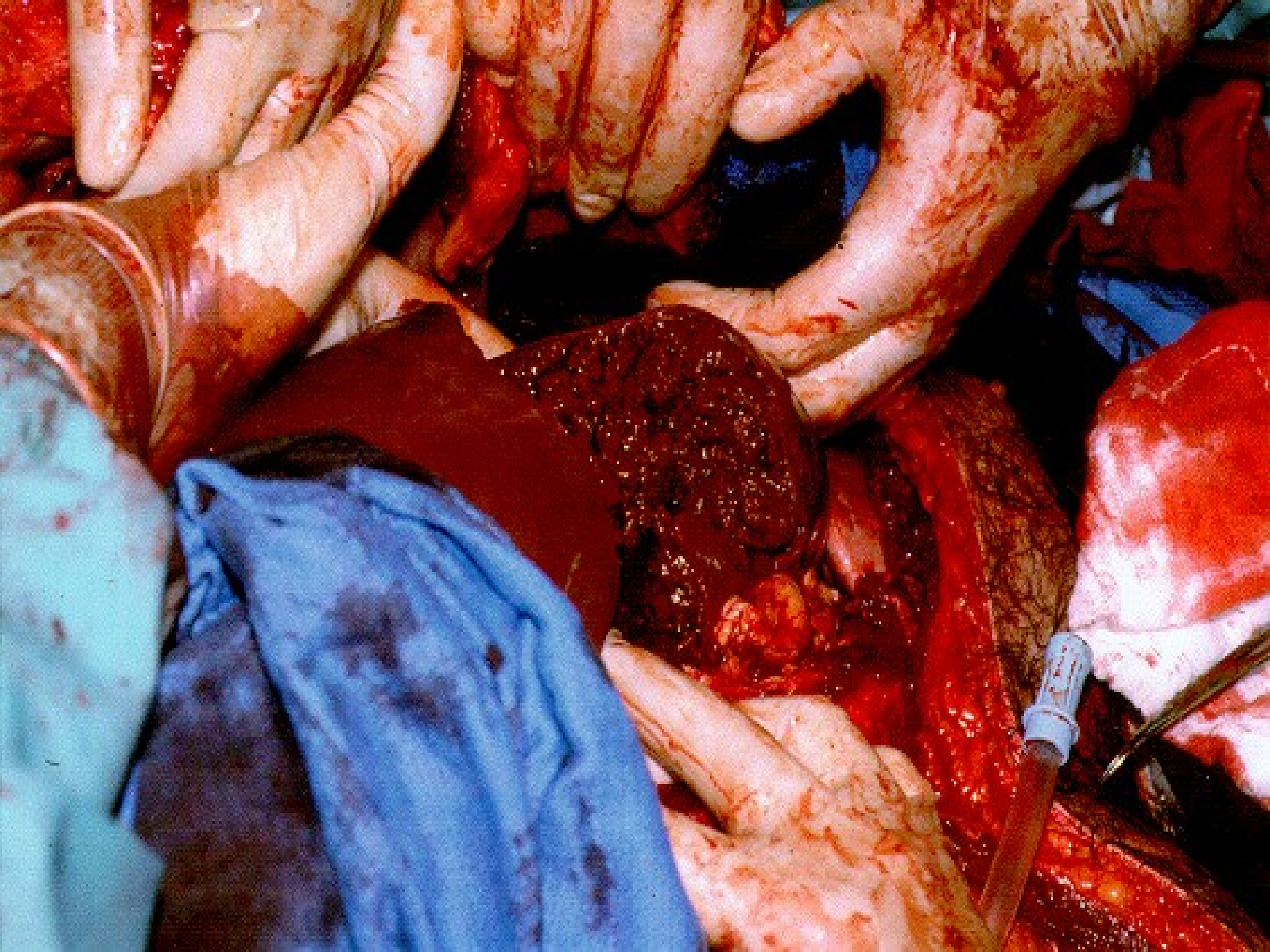
## Late

- Systolic BP > 100 mmHg
- Heart rate < 100 bpm
- pH = 7.40
- Hematocrit > 20%
- Urine output normal
- Mentation normal
- Cardiac output normal or high

McCunn M, Dutton R: Endpoints of Resuscitation. *Curr Opin Anes* 2001

# **Early Management: Surgical**

- **Rapid diagnosis of hemorrhage**
- **Rapid therapy to control hemorrhage**
  - **operative**
  - **angiographic embolization**





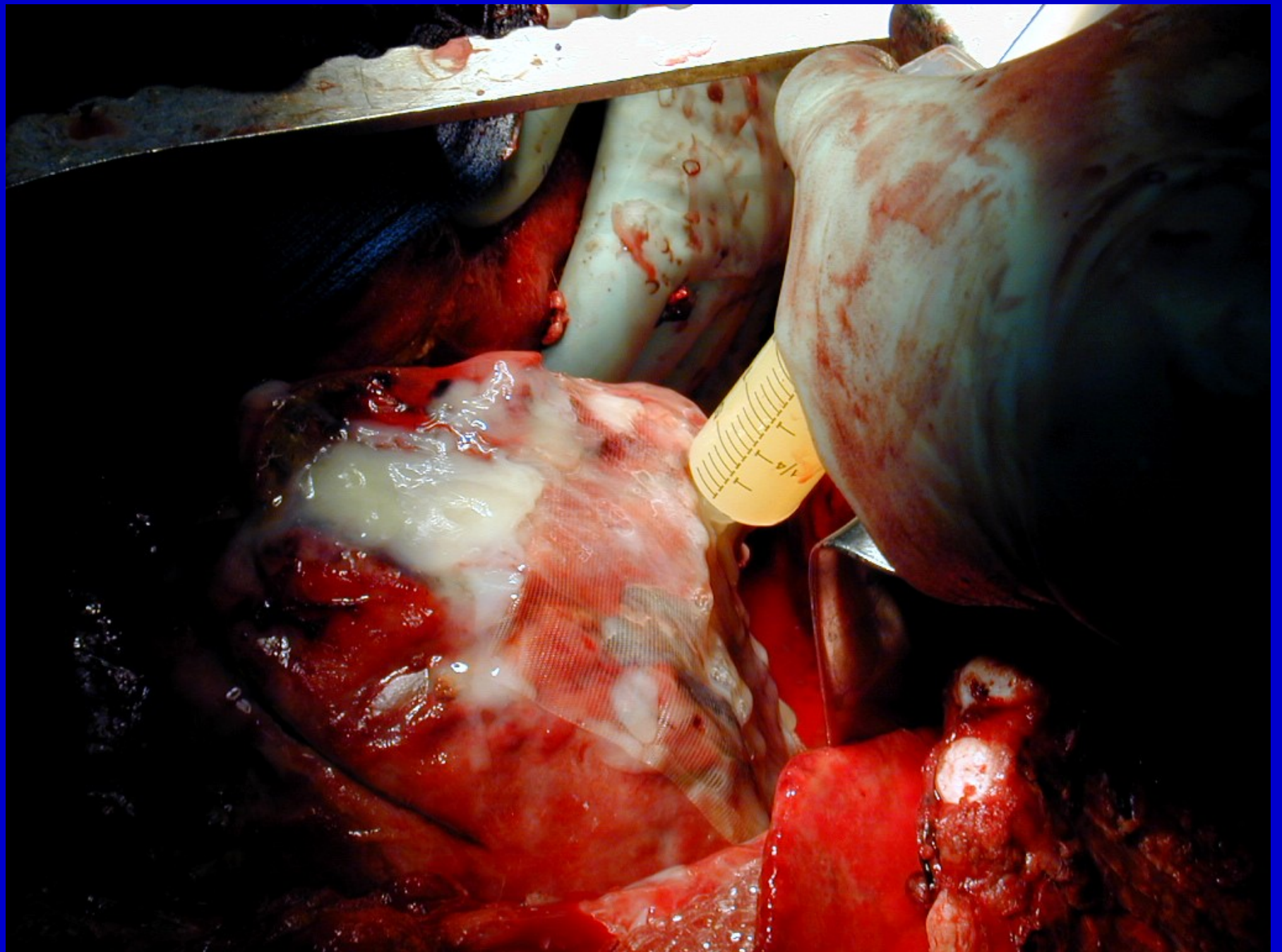
# **Early Management: Surgical**

## **Damage control**

- **Anticipate failure of standard methods**
- **Hypothermia and coagulopathy**
- **Acidosis and metabolic abnormalities**

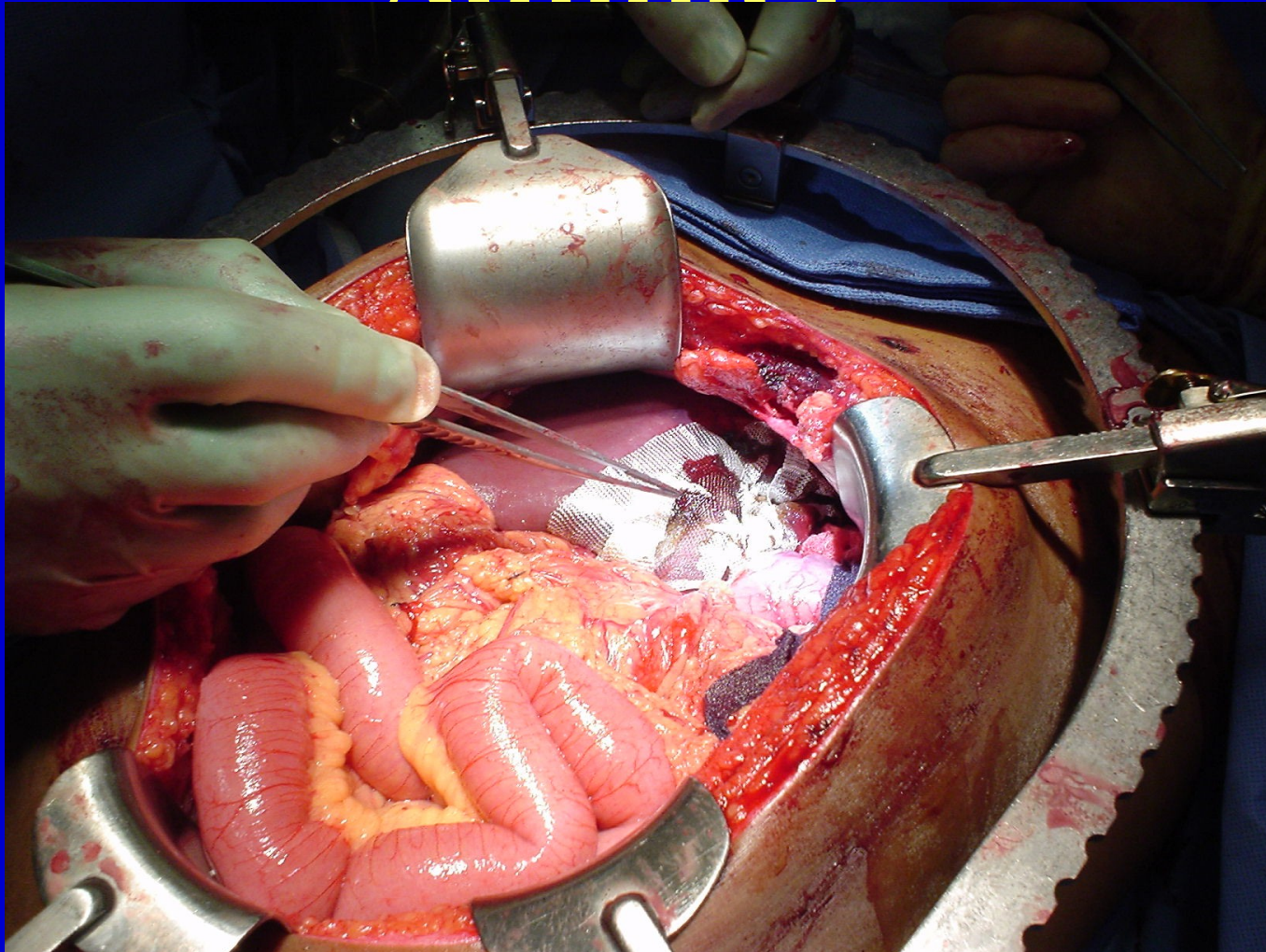
## **Principles of damage control**

- **Obtain best possible surgical hemostasis possible in a timely fashion**
- **Temporize hollow viscus injury**
- **Pack coagulopathic bleeding**
- **Resuscitate and correct hypothermia**





# Hemorrhage Control Adjunct



# Hypothermia

## ● 1° causes

- Exposure
- IV fluids
- Irrigation

## ● 2° causes

- Temperature regulation under anesthesia
- Shivering paralyzed
- Metabolism impaired
- Dry, cold anesthesia gases

# Complications of Hypothermia

- Hypothermia (core temperature < 35°C)
  - Impairs myocardial contractility
  - Impairs coagulation
  - PT and APTT prolonged at 34°C
  - PT and APTT increases with each incremental decrease in temperature

Rohrer MJ et al. *Crit Care Med.* 1992;20:1402-1405.

# Complications of Hypothermia

- **Induces thrombocytopenia**
  - Hepatic and splenic sequestration
  - Increased bleeding time
    - Reversed by rewarming
- **Accelerated fibrinolysis**
- **Reduced enzyme kinetics**
- **Abnormal platelet aggregation**
  - Surface molecule expression reduced

Hessell EA, et al. *J Surg Res* 1980; 28:23

Michelson AD, et al. *Thromb Haemost* 1994;71:633

Yenari MA, et al. *Throm Res* 1995; 77:47

Johnson TD, et al. *J Trauma* 1994; 413-4

# Acute Complications

## ● Coagulopathy

- **Dilutional**
  - Washout of factors
  - Depletion of platelets
- **Hypothermia-induced**
  - Prolongation of PT and APTT
  - Platelet dysfunction

# Trauma - Associated Coagulopathy

**Single blood volume (BV) replacement**

- ~ 40% of pre-transfusion platelets remain

**Fibrinogen most sensitive to dilution**

- ~ 50% reduction @ 1.5 BV replacement

- **Critical levels of prothrombin, platelets, FV, FVII by**

**2.5 BV replacement**

- Hippala ST, et al. *Anesth Analg* 1995; 81:360-5



**Trauma -  
Associated  
Coagulopathy  
Hemorrhage**



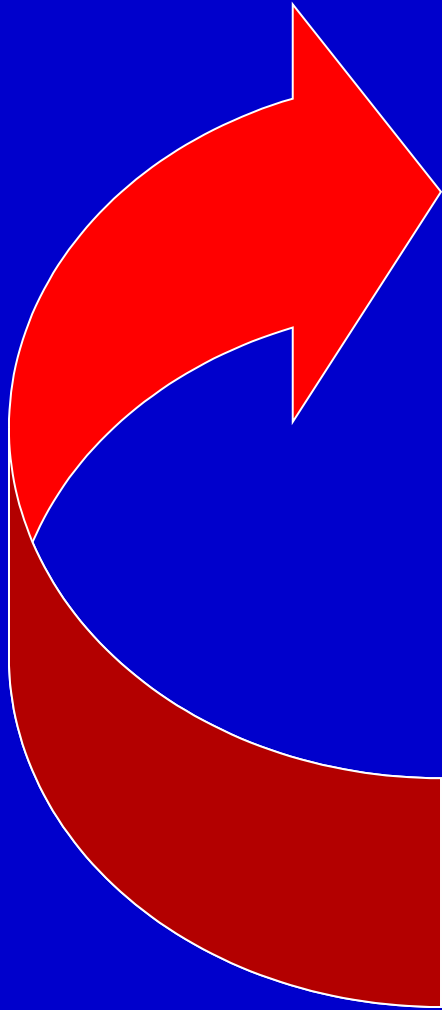
**Massive transfusion**

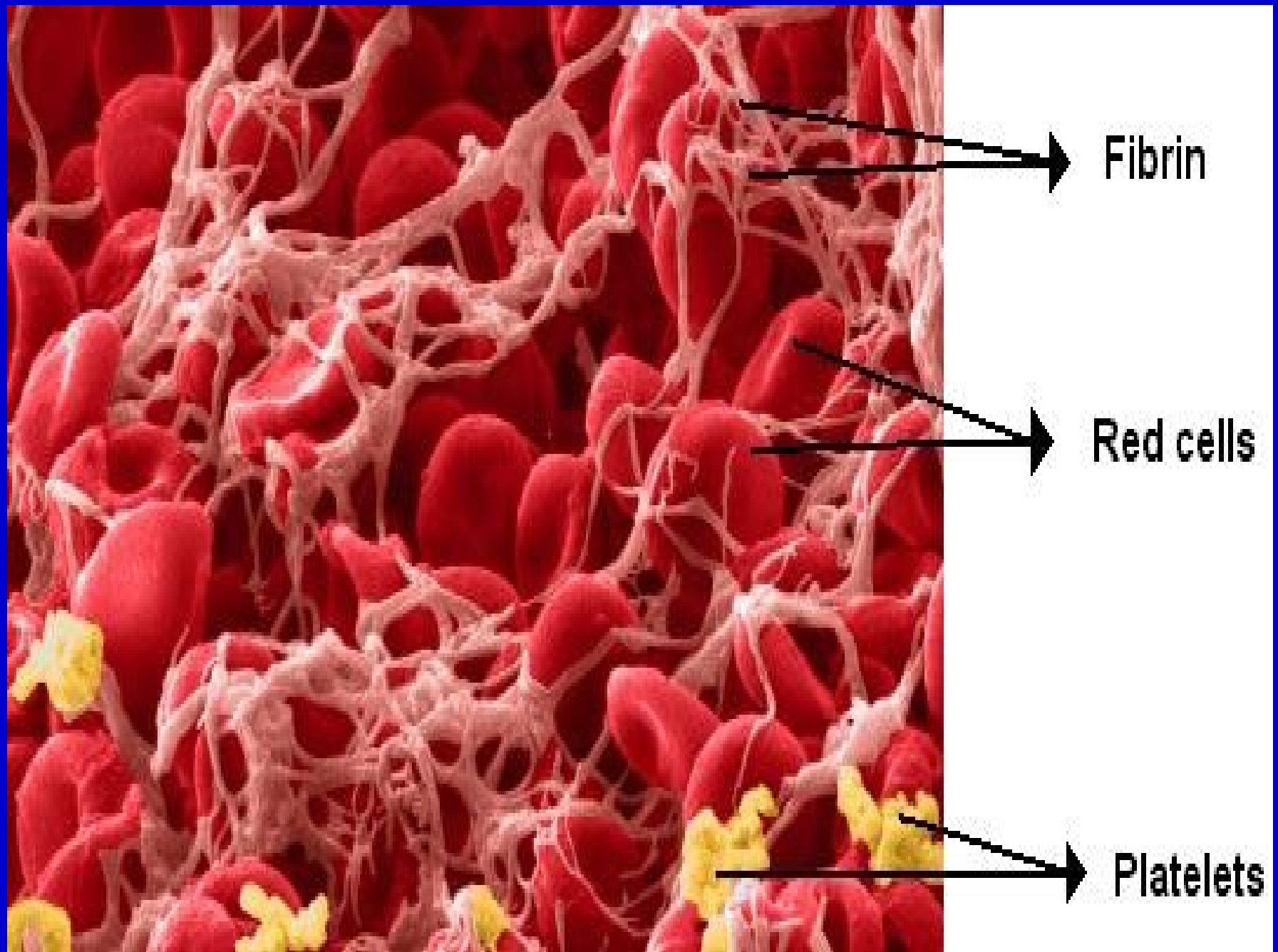


**Hypothermia**

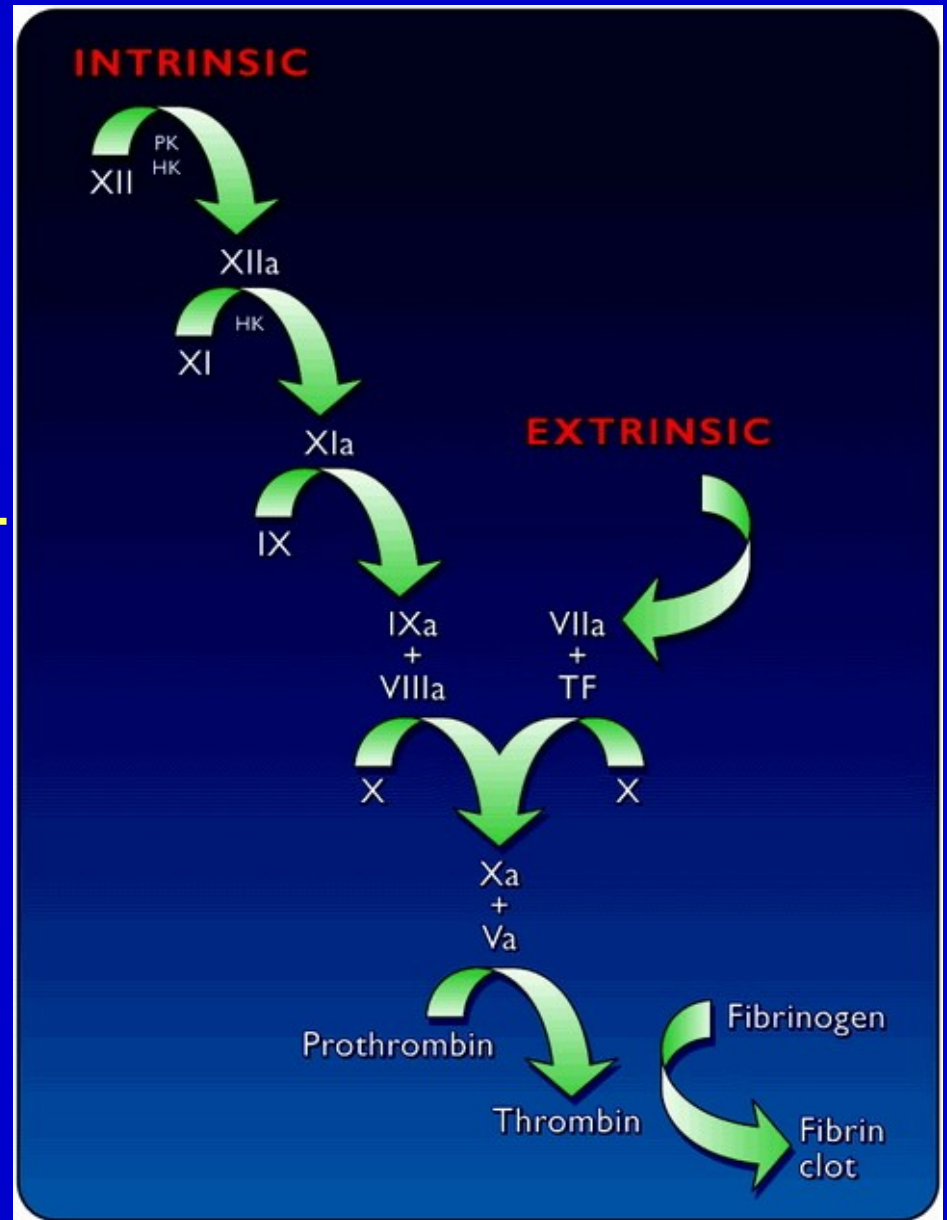
**Acidosis      $\Delta$**

**Coagulopathy**

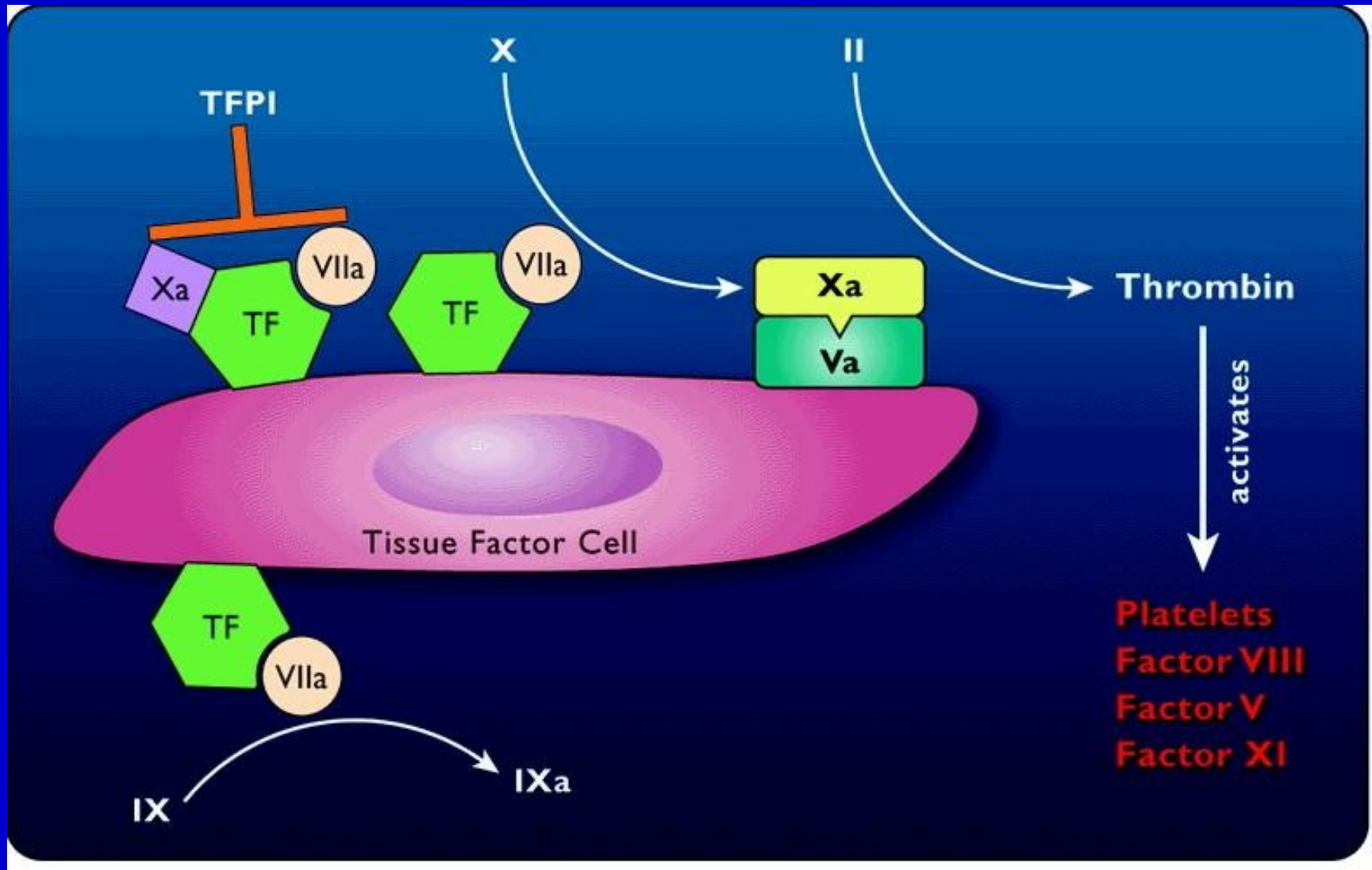




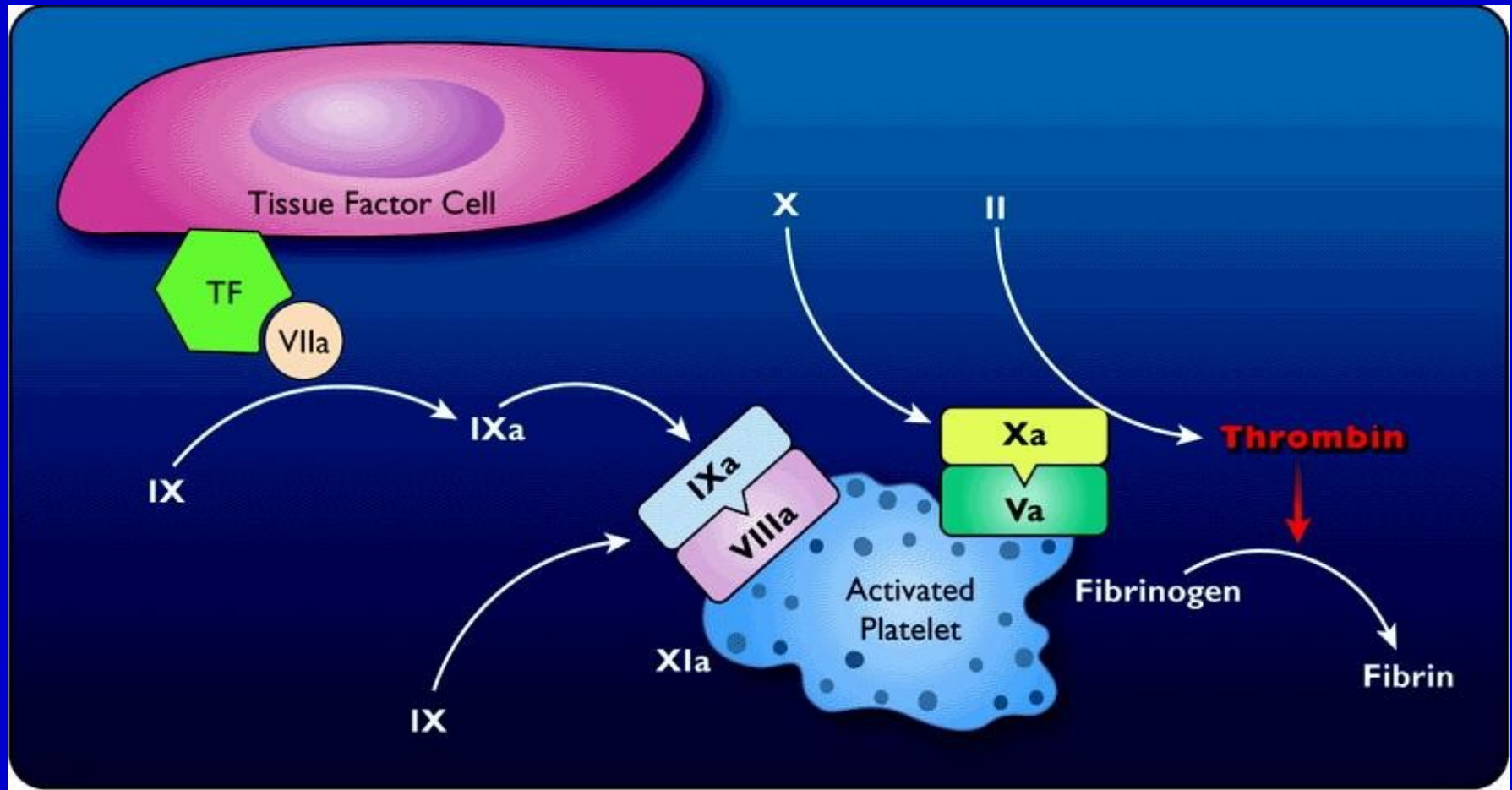
# Coagulation Cascade



# Initiation/Amplification



# Amplification/Propagation



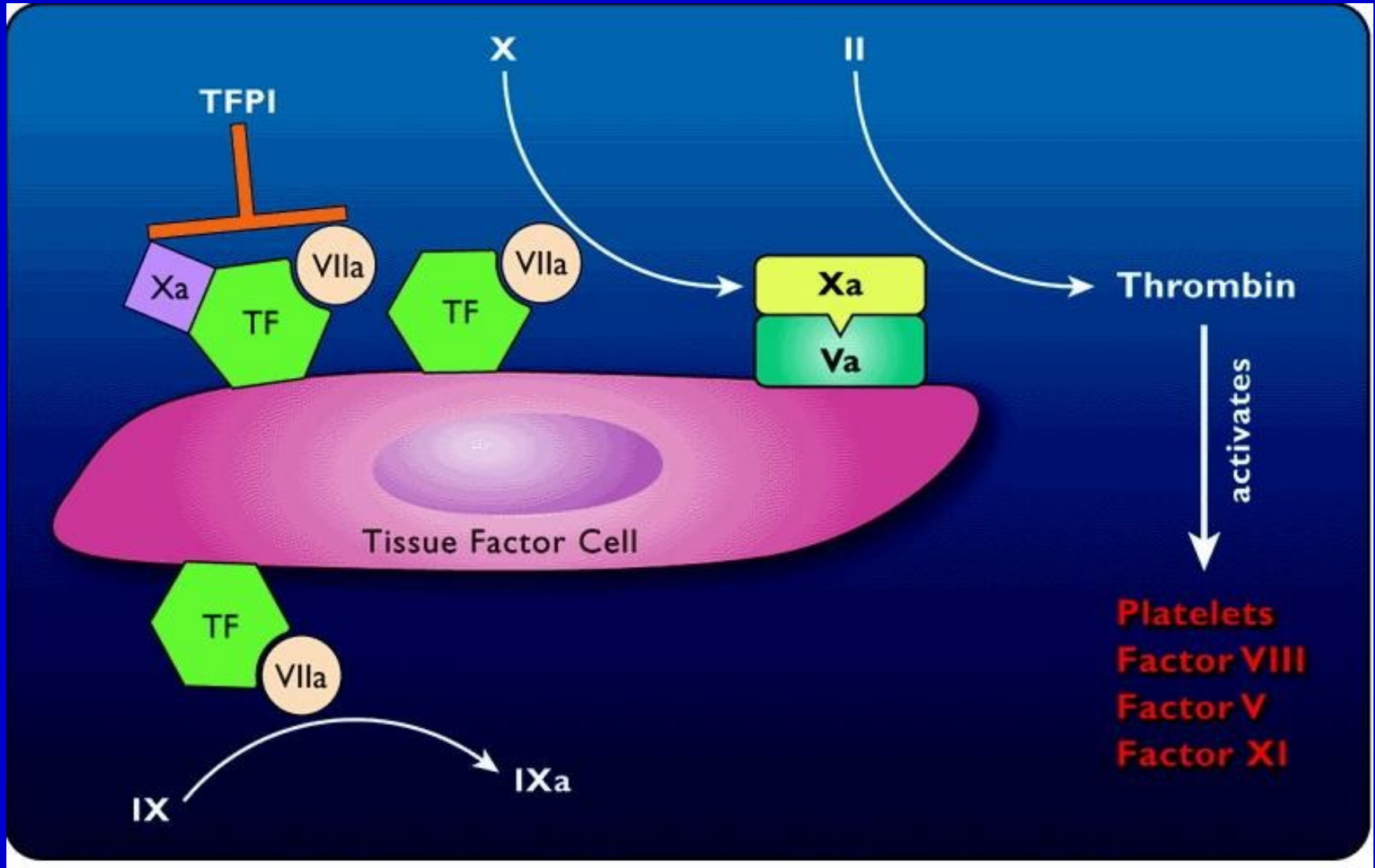
# **Factor VIIa (rFVIIa)**

- **Recombinant human product produced using hamster kidney cells**
- **Single manufacturer in Denmark**
- **In adults 1/2 life of 2.7 hours**
- **In therapeutic doses, requires only Factor I (Fibrinogen), II (Thrombin) and platelets (50K minimum) to produce clotting**
- **In U.S. licensed only for use in hemophiliacs with inhibitors to Factor VIII or IX**

# **rVIIa M.O.A.**

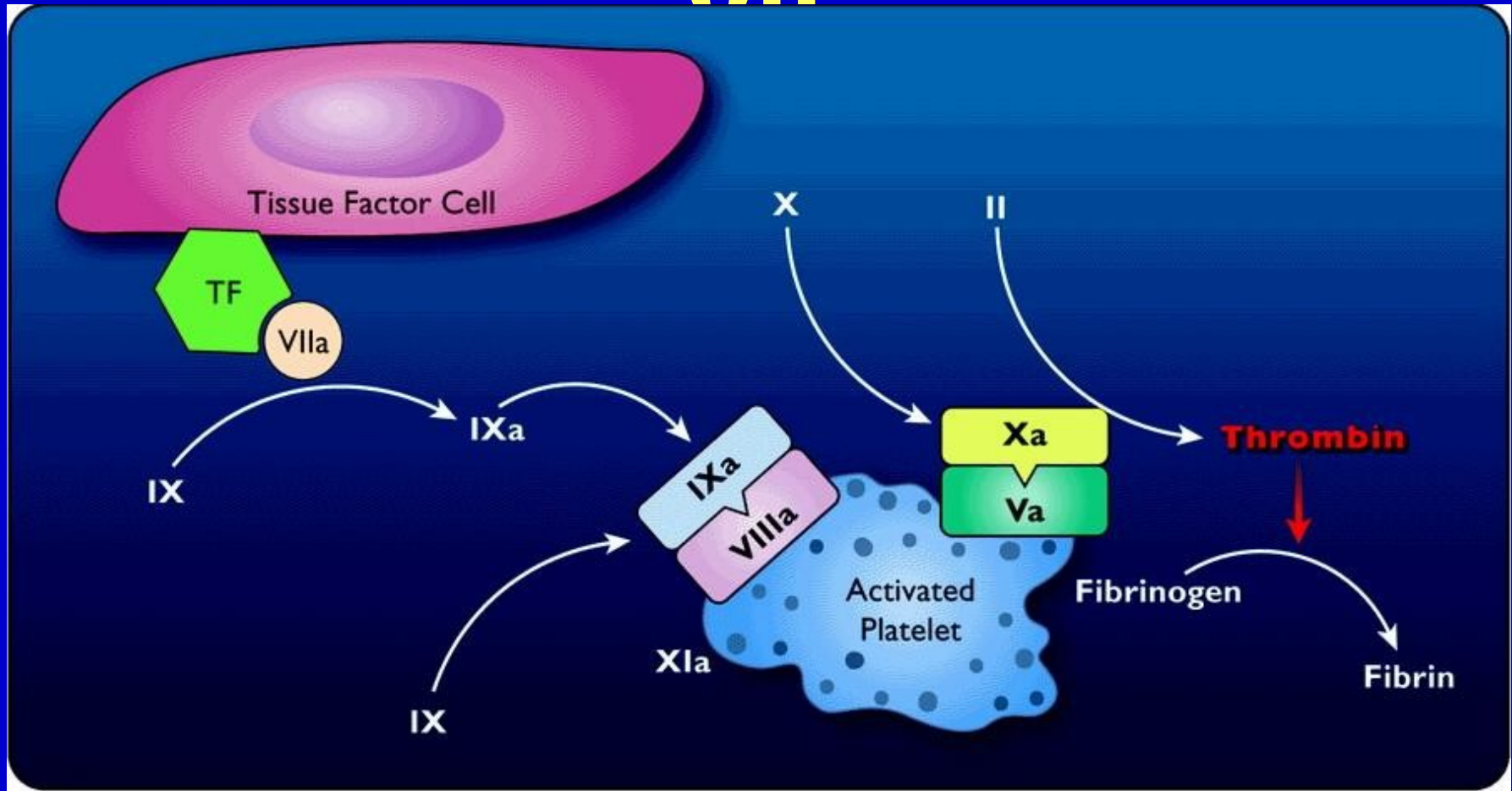
- **Dual mechanism of action**
- **TF dependent pathway**
  - **rVIIa binds TF on TF bearing cell, activates factor X resulting in production of thrombin**
- **TF independent pathway**
  - **rVIIa binds activated platelets and on the surface of the platelet activates factor X**
  - **newly formed Xa binds Va from the activated platelet forming “prothrombinase”**
- **Both pathways occur only at site of injury**

# Initiation/Amplification





# Amplification/Propagation



# Off-label Uses

- **Hepatectomy**
- **Hepatic transplant**
- **Cirrhotic GI hemorrhage**
- **Traumatic hemorrhage**
- **Stem-cell (bone-marrow) transplant**
- **Congenital or acquired factor deficiencies**
- **Thrombocytopenic conditions**
- **Reversal of Coumadin therapy**
- **Fulminant liver failure**
  - **Peri-procedure**
- **Hemorrhagic cystitis**
- **Traumatic brain injury (adults)**
- **Prevention of intra-ventricular hemorrhage (neonates)**
- **Cardiac surgery**

# rVIIa use in Surgical Patients

- 36 pts randomized to 20ug/kg, 40ug/kg & placebo
- Average blood loss : 1235 ml, 1089 ml, 2688 ml (p<.001)
- # pts transfused: 3/8 0/16 7/12
- rFVIIa reduces perioperative blood loss and eliminates need for transfusion in patients undergoing major surgery

Friederich P, Henny C, Messelink E, *et al*: "Effect of rFVIIa on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial." *Lancet* 2003; 18:201-5.

# **rVIIa use in Surgical Patients**

- Case series 21 patients
- Cardiovascular surgery, trauma, liver transplantation

## **BEFORE rFVIIa**

- 22 U prbc's
- INR 1.6
- PTT 40 sec

## **AFTER rFVIIA**

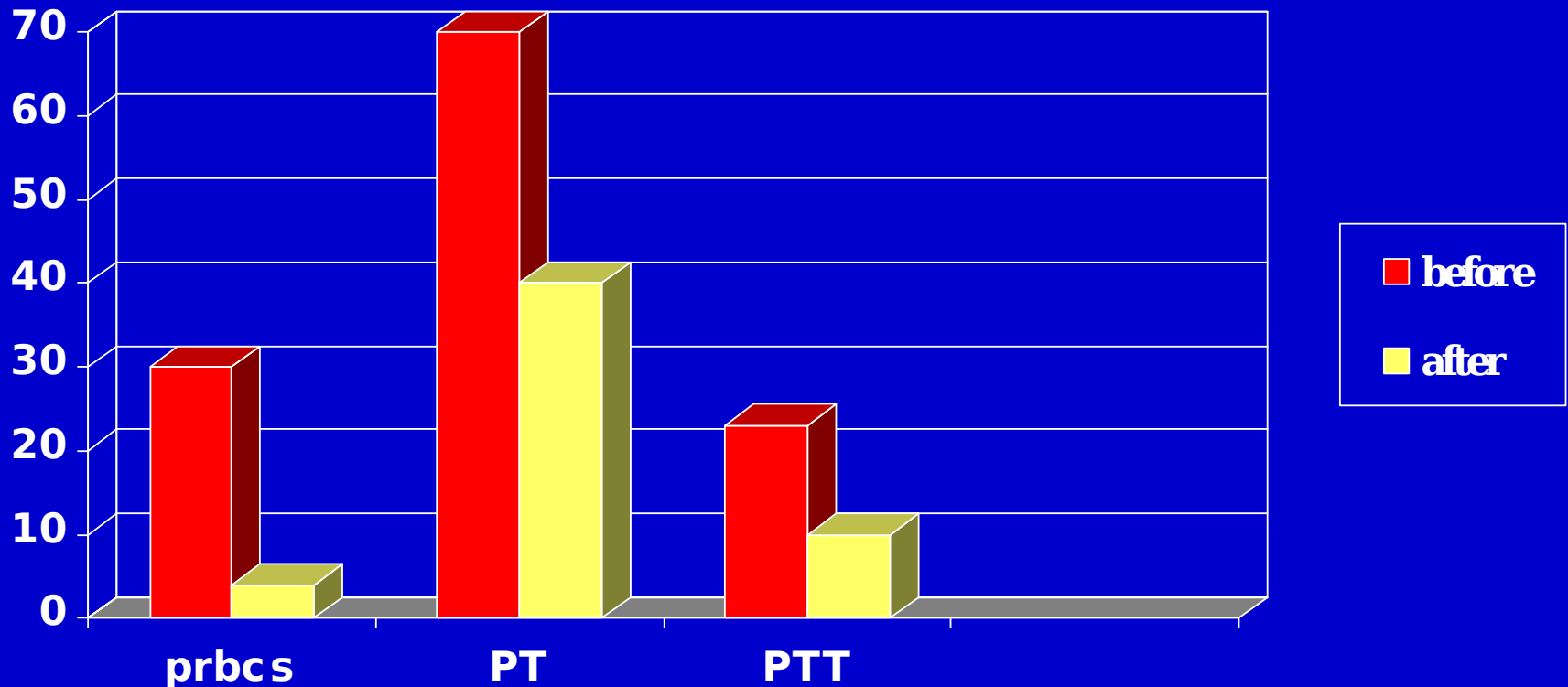
- 2 U prbc's
- INR 1.0
- PTT 40 sec

**Eikelboom JW, *et al*: Recombinant FVII for the treatment of life threatening Hemorrhage. *Blood Coagul Fibrinolysis* 2003;14:713.**

# **rVIIa in Trauma Patients**

- **19 critically ill, multi-transfused patients  
(10 blunt / 9 penetrating)**
- **Given 1 - 3 doses rFVIIa  
(195  $\pm$  113 mcg/kg needed to stop  
hemorrhage)**
- **15/19 patients responded**
- **Decrease in PRBCs, PT and PTT (p = < .05)**
- **68.4% survival (13/19 patients)**

# rVIIa in Trauma Patients



**Martinowitz U: Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. *Can J Anaesth* 2002;49:S15-S20.**

# Shock Trauma Center experience with rFVIIa



**Dutton RP, McCunn M, Hyder M,  
*et al:***

**Factor VIIa for Correction  
of Traumatic Coagulopathy.**

***Journal of Trauma, Oct 2004.***

# Shock Trauma Centre experience with rFVIIa

- 81 patients
- Indications:
  - Acute post-traumatic hemorrhage (46)
  - Severe traumatic brain injury (20)
  - Septic coagulopathy (4)
  - Congenital Factor deficiency/ Warfarin therapy (11)
- Off-label use, controlled by 'Gatekeeper'





**Anatomic region of single most significant injury (most patients were bleeding from multiple sites at the time of FVIIa administration)**

● Brain	31	● Abdomen	32
● Face	1	● Inferior Vena Cava	7
● Neck or spine	3	● Liver	7
● Chest	9	● Spleen	2
● Lungs	4	● Mesentery / Bowel	3
● Heart	3	● Pelvis	7
● Thoracic Aorta	2	● Aorta / Iliac Artery	6
● Extremities	5		

# Mechanisms of injury

## Blunt Trauma: 59

- Motor vehicle collision 25
- Motorcycle collision 8
- Pedestrian struck 8
- Fall from standing 8
- Fall from height 3
- Industrial explosion 3
- Assault 2
- Crush 1
- Other 1

## Penetrating trauma: 22

- Gunshot 19
- Stab 3



# Blood product utilization in the 24 hours before and after FVIIa

## administration

**Responder  
(n = 61)**

**Non-Responder  
(n = 20)**

<b>RBC before</b>	<b>15.0 +/- 14.8</b>	<b>26.7 +/- 12.8</b>	<b>p = 0.002</b>
<b>RBC after</b>	<b>4.5 +/- 8.0</b>	<b>22.6 +/- 14.7</b>	<b>p = 0.00002</b>
<b>Plasma before</b>	<b>11.6 +/- 10.6</b>	<b>13.7 +/- 10.1</b>	<b>p = 0.42</b>
<b>Plasma after</b>	<b>4.6 +/- 8.2</b>	<b>20.8 +/- 15.6</b>	<b>p = 0.0002</b>
<b>Platelets before</b>	<b>2.2 +/- 2.8</b>	<b>1.5 +/- 1.2</b>	<b>p = 0.13</b>
<b>Platelets after</b>	<b>1.5 +/- 2.6</b>	<b>4.5 +/- 4.2</b>	<b>p = 0.007</b>
<b>Total before</b>	<b>28.8 +/- 25.9</b>	<b>41.9 +/- 22.4</b>	<b>p = 0.03</b>
<b>Total after</b>	<b>10.6 +/- 17.6</b>	<b>47.8 +/- 32.5</b>	<b>p = 0.00006</b>

# Coagulation parameters

	Before	After	<i>p</i> -value
PT	17.5	9.3	< 0.001
INR	2.2	0.58	0.001

# **Outcome of rFVIIa therapy**

- **75% initial response rate**
- **Overall ~ 50% survival in treatment group**
- **More useful earlier ? Activity impaired in presence of severe acidosis and/or hypothermia**
- **Better outcome in absence of shock**
  - **traumatic brain injury**
  - **factor deficiency**
- **Cost benefit analysis - gross cost, total blood product utilization, unmeasured benefits**

# Dose Recommendation

- Hemophilia

- 90 mcg/kg bw

- Trauma

- First dose: 120 mcg/kg
- Second dose: 60-90 mcg/kg
  - For no effect in 20 minutes after dose 1

- TBI

- 20 mcg/kg

# Dose Recommendation

- Trials currently 80-180 mcg/kg
- Dose escalation schemes
- Continuous infusion NOT recommended
- 9.6 mg (100 mcg/kg in 70 kg adult)
  - \$5000-\$6000

# **Complications/Side Effects**

## **Thrombosis**

- no intravascular thromboses at trauma autopsy  
(brain, hepatic, small bowel, lung)
- no MI, pulmonary embolism, vascular graft occlusion, ischemic stroke up to 7 days after treatment
- overall rate of abnormal thrombosis 0.8%
- most occur in hemophiliacs receiving multiple



# Unanswered Questions

- **Timing of administration**
  - Pre-op versus intra-op versus post-op
  - Up front versus conventional method (failure)
- **Correct initial dose**
- **Correct subsequent dose(s)**
- **Predictors of futility/usefulness**
- **Impact on morbidity/mortality**

# Summary

- **Massive hemorrhage and resuscitation**
- **New model of Cell based coagulation**
- **rVIIa**